Role of BRCA1 in brain development.

Journal: Proc Natl Acad Sci U S A

Publication Year: 2014

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PubMed link: 24639535

Funding Grants: Curing Hematological Diseases

Public Summary:
BRCA1 mutations predispose women to breast and ovarian cancer. Women in families that have BRCA1 mutations the lifetime risk of breast and or ovarian cancer can be upwards of 90%. Although best known for it's function in preventing breast cancer, we observed large amounts of BRCA1 gene being expressed in neural stem cells. To test if this presence was important we removed the BRCA1 gene in stem cells of the developing brain. The animals without BRCA1 showed numerous defects throughout the brain including areas involved in the processing of the sense of smell, movement control and memory formation among others. This conclusively showed that BRCA1 is required for the normal healthy development of the brain. Neural stem cells give rise to all the different cell types of the brain. Our experiments show that BRCA1 affected neurons, which are the cells that make up the computational component of the brain the most. The lack of BRCA1 makes neural stem cells unable to mature to become neurons, whereas supportive cells like astrocytes are not affected. Much of the brain defects that we observed could be attributed to neural stem cells dying by a process of induced cellular suicide in neural stem cells or when they are on their path to become neurons. This cellular suicide named apoptosis occurs when the cells that something is so profoundly wrong that they deem it impossible to overcome the problem in them. Our investigations showed that the likely insult that ultimately killed the cells without BRCA1 was related to breaks in their DNA. This we know because when we combined the mutation with BRCA1 with that one of the gene p53 that made it more difficult to execute the cellular suicide program, the extent of brain damage was lessened. When we combined the mutation with BRCA1 with that of the gene ATM, which allow cells to sense DNA damage, we saw no discernable brain defect. This suggests that if cells cannot notice the DNA damage, they will not trigger the suicide program. What we can conclude from this work is that the gene BRCA1 gene is important for the formation of a healthy brain and that the presence of BRCA1 is likely to protect the DNA from neural stem cells that allow the formation of the complete brain. In the absence of BRCA1, stem cells from the brain will commit cellular suicide when they are about to become neurons, the computational units of the mammalian brain. These results could explain how brains evolved through evolution and how management of DNA damage can be used to make brains bigger or smaller.

Scientific Abstract:
Breast cancer susceptibility gene 1 (BRCA1) is a breast and ovarian cancer tumor suppressor whose loss leads to DNA damage and defective centrosome functions. Despite its tumor suppression functions, BRCA1 is most highly expressed in the embryonic neuroepithelium when the neural progenitors are highly proliferative. To determine its functional significance, we deleted BRCA1 in the developing brain using a neural progenitor-specific driver. The phenotype is characterized by severe agenesis of multiple laminated cerebral structures affecting most notably the neocortex, hippocampus, cerebellum, and olfactory bulbs. Major phenotypes are caused by excess apoptosis, as these could be significantly suppressed by the concomitant deletion of p53. Certain phenotypes attributable to centrosomal and cell polarity functions could not be rescued by p53 deletion. A double KO with the DNA damage sensor kinase ATM was able to rescue BRCA1 loss to a greater extent than p53. Our results suggest distinct apoptotic and centrosomal functions of BRCA1 in neural progenitors, with important implications to understand the sensitivity of the embryonic brain to DNA damage, as well as the developmental regulation of brain size.

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